- **OSHA Regulated Compounds** The chemical substances used as ingredients in the manufacture of Xenical capsules are listed in Appendix D. Copies of available MSDS's are included in Appendix D [Confidential]. Manufacturing of Xenical capsules is in accordance with applicable OSHA regulations.

- **Statement of Compliance** A compliance certificate signed by a high ranking company official certifying that the manufacture of Xenical capsules:

  1. will be in compliance with all local and national environmental laws
  2. will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
  3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.6.d <u>Discussion of the Effect of Approval on Compliance with Current Emission Requirements</u>

Manufacture of the Xenical capsules at Nutley site is not likely to have a significant impact on compliance with current emission requirements, since the majority of waste will be in solid form, which will be incinerated by a licensed incineration facility regulated by the NJDEPE and/or EPA. A small quantity of the drug substance and other excipients is likely to be released in the wastewater due to equipment washdowns. However, the quantity released into wastewater is going to be a small amount which will not cause any significant impact on the wastewater discharge limits. Therefore, approval and subsequent increase in production of the drug product at the Nutley site is not expected to affect compliance with current emission requirements.

## 6.6.e Expected Introduction Concentrations

The projected annual production volume based on five-year production estimates is provided in the confidential Appendix E. The expected introduction concentrations from use and disposal are calculated based on the 5th year projected estimates.

### I. Expected Introduction Concentrations from Use

The expected introduction concentration (EIC) entering into the aquatic environment from patient use was calculated as follows:

EIC - Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liter per day entering POTW's*
C = year/365 days
D = $10^6$ mg/kg (conversion factor)

* [redacted] entering publicly owned treatment works (POTW's), as cited in "Guidance for Industry: for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by Center for Drug Evaluation and Research (CDER), November 1995.

The actual calculation is shown in confidential Appendix F. The EIC was calculated, assuming that all the drug substance produced is used, even distribution through the U. S. per day, and no metabolism or depletion mechanisms exists. The criteria for [redacted] are met.

The drug is not likely to enter the terrestrial environment in a significant amount through usage except where reclaimed sludge is applied to the land. In U.S., the reclaimed sludge is usually incinerated, therefore the drug substance is not likely to present in significant quantity to cause detrimental effects in the terrestrial environment.

ii. Expected Introduction Concentrations from Disposal

During the manufacture of the drug product, the majority of pharmaceutical waste will be disposed of as solid/liquid waste. As mentioned under item 4e, the pharmaceutical waste will be disposed of by incineration, therefore the EIC arising from disposal is not likely to be in significant quantity to have any impact.

## 7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

This environmental assessment is filled pursuant to 21 CFR 25.31 a(a) which does not meet the circumstances (criteria) described in Tier O approach mentioned in the document entitled, "Guidance for Industry: for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by the Center for Drug Evaluation and Research (CDER), November 1995. Therefore, additional information is provided under item 7 of this environmental assessment.

### Summary of Absorption and Metabolism of Orlistat

Orlistat is a quasi-irreversible, specific inhibitor of lipases, especially gastric, pancreatic and carboxyl ester lipase, but also hepatic lipase and lipoprotein lipase. It acts by opening of the β-lactone ring and forming an ester bond with the hydroxygroup of the active site serine of the lipases. Orlistat limits fat absorption by inhibiting the release of free fatty acids from the triglycerides which as such are not absorbed to a significant extent. Therefore, its site of action is the gastro-intestinal tract and systemic absorption is not necessary for its therapeutic effect.

Absorption from the gastro-intestinal tract is slow, and varies from a few percent to at most 20% of the dose, depending on the formulation and the feeding conditions of the animals. In man absorption from the capsule formulation can be estimated to be <10% of the dose. Most of the unabsorbed material is excreted unchanged with the feces, but the small proportion of the Xenical dose which is absorbed is extensively metabolized presystemically. At therapeutic dose levels in man and up to about 25 mg/kg/day in animals no parent drug could be detected in the systemic circulation. Bioavailability of the oral dose is <1%. The primary site of absorpton is the gut wall. Of the bioavailable dose, the hydrolytic opening of the beta-lactone ring yielding metabolite M1 is the primary biotransformation process leading to loss of lipase inhibiting activity. Another metabolite M2 due to

hydrolysis of the leucine ester bond is expected, however, it has not been detected. Further biotransformation follows the fatty acid metabolism pathway leading to branched chain dihydroxy-dicarboxylic acids which are excreted in bile and urine as such or as lactones or glucuronide conjugates. The above summary of absorption and metabolism has been prepared from a technical report entitled "Update on Summary of ADME Data of Orlistat in Humans and Experimental Animals. Status end 1993 (For presentation to FDA at preclinical end of Phase II meeting)". A copy of the entire report is included in Appendix G.

Based on the above mentioned findings, there is no single metabolite other than the parent drug substance, constituting greater than 10% concentration, that is likely to be released in the environment through usage by patients. Therefore, the environmental fate of the only parent drug substance is discussed.

The present NDA for Xenical is for the therapeutic use of it in the treatment of obesity. This drug will be made available for therapeutic use in oral formulations through physician prescriptions.

7. (i) **Identification of Substances of Interest**: Based on Absorption, Distribution, Metabolism and Elimination (ADME) studies, less than 10% of the oral dose is absorbed depending upon formulation and the feeding conditions of the animals. Most of the unabsorbed dose is excreted unchanged in the feces. The bioavailable dose is metabolized and excreted via bile and urine as lactones or glucuronide conjugates. At the therapeutic dose in man the bioavailability is less than 1%. Therefore, there is no single metabolite or structurally related substances (SRS's) constituting greater than 10% that is expected to be released in the environment except the unchanged parent drug substance. This environmental assessment will only address the environmental fate and effects of the parent drug since it is the predominant moiety (greater than 90%) entering the environment through usage. The parent drug is not likely to be acutely or chronically toxic. The rat oral $LD_{50}$ is greater than 5000 mg/kg. There were no signs and symptoms of overt toxicity observed during the observation period. It is not a mutagenic, reproductive or teratogenic compound (Appendix A).

7. (ii) **Physical/Chemical Characterization:** The physical/chemical properties of the drug substance are described in appendix A. The n-octanol/water partition coefficient ($K_{ow}$) was calculated based on the

solubility determination in water and n-octanol separately. The calculated $K_{ow}$ for Orlistat was 4.4; therefore, [redacted] criteria were utilized for environmental fate and effect studies.

7. (iii) **Environmental Depletion Mechanisms:** The aerobic biodegradation study was performed with Orlistat drug substance. Details of the study are provided under item 7.(v)c.5. The calculation of Maximum Expected Emitted Concentration (MEEC) and Expected Environmental Concentration (EEC) were based on the assumption of no depletion mechanisms.

7. (iv) **Expected Environmental Concentration (EEC):** The calculation of MEEC and EEC is shown in Appendix F.

7. (v) **Summary:** The environmental fate and effects of Xenical in various compartments is discussed below.

7.(v) (a) **Air:**

The active drug substance is manufactured by F. Hoffmann-La Roche Co., Basle, Switzerland in accordance with applicable laws. The final dosage form will be manufactured at the Hoffmann-La Roche Inc. facility located in Nutley, New Jersey.

Potential air emissions consist of minor amounts of pharmaceutical [redacted] into [redacted] equipment. Emission of particulate matter is controlled by means of [redacted] filter dust collectors. All equipment operates in compliance with current requirements for particulate emissions. Based on the experience with similar products for operations involved with the production of capsules, approximately [redacted] percent of the materials go to form finished product. Based on the estimated maximum annual production volume provided to the FDA in the confidential Appendix E, only a small amount is expected to be released in the air.

Of the 5 percent expected release, the majority is in the form of solid waste due to material cleaned up from equipment or the [redacted] filter dust collectors which service them. Control efficiencies for [redacted] filter dust collection is in excess of [redacted] which will further reduce the amount expected to be released in the air. The waste will be incinerated. Therefore, it is not expected to be released in the air in significant amounts to cause detrimental effects during the

manufacturing of Xenical drug product. The workers will be protected by engineering controls and/or use of personal protective equipment.

The drug is not likely to be released in the air through usage except accidental spill (breakage of capsules) situations. Even in such a remote situation the drug is not likely to be released into the ambient air due to its physical form. A minute environmental release of the drug is also expected to be dispersed in the ambient air so that concentrations per cubic meter of air would be extremely small (probably in ppt range) to cause any adverse environmental impact.

There are no direct acute and subchronic toxicological studies available to evaluate the toxicological effects of low level inhalation exposure to Orlistat. However, ADME studies in animals and man indicate that the drug is very poorly absorbed via the intestinal tract. Also, it may not be absorbed in significant amount via inhalation. Animal studies also indicate relatively low toxicity. For example, acute oral $LD_{50}$ in rat is greater than 5,000 mg/kg indicating low acute toxicity. It is not a mutagenic drug in various mutagenic assays. It is not teratogenic or a reproductive toxicant (MSDS, Appendix A).

**Based on available pharmacological and toxicological studies as well as physical chemical properties and production volume, the drug substance is not likely to persist in the ambient air to cause any significant adverse environmental impact.**

7.(v) (b) Aquatic Environment

The wastewater from Xenical capsules manufacturing process consists mainly of equipment washdowns. The wastewater from the capsules manufacturing operations contains residual amounts of active ingredients along with excipients used in the manufacturing of drug products. As mentioned above under (item 7 (v)(a) air) most of the loss will be in the form of solid waste. The releases to the water consist of the small quantity of material which is washed from the various types of equipment after the majority of the material has been removed by normal means such as dry vacuuming.

Based on the estimated maximum annual production volume provided to the FDA in the confidential Appendix E, only small amounts (probably [redacted] are expected to be released in the water. The wastewater effluent from the Xenical capsule manufacturing process is combined with wastewater from other manufacturing processes and

discharged through a pretreatment system to the Passaic Valley Sewage Commission (PVSC) treatment plant (a POTW), which is equipped to process 300 million gallons per day. **The expected released drug from the manufacturing site would be diluted to a concentration below that of significant concern.**

Following therapeutic use, minute concentrations of the drug and its metabolites will be released into sewage through fecal and urinary excretions.

In order to evaluate the impact of the very low concentration of Orlistat expected to enter the aquatic environment, we determined the concentrations of Orlistat that must be attained before toxic effects are observed.

**In aquatic species the following studies were conducted to evaluate its effects.**

1. Daphnia magna acute toxicity

The acute effects of Orlistat on the fresh water invertebrate water flea, Daphnia magna, were evaluated under static conditions according to the FDA Environmental Assessment Technical Assistance 4.08.

Based on the results of the range finding study, nominal concentrations selected for definitive tests were 1.56, 2.59, 4.32, 7.20, 12 and 20 mg/L. Samples were collected at 0, 24 and 48 hours for analytical confirmation. The overall mean measured concentrations were [redacted] Twenty neonates were exposed to each concentration for 48 hours. The 48 hour median effective concentration (EC50), the concentration of Orlistat estimated to result in immobilization or death to [redacted] percent of the test population was calculated to be [redacted] mg/L. The 48 hour No Observed Effect Concentration (NOEC) was [redacted] mg/L. This study was performed according to the FDA Good Laboratory Practices (GLP) Guidelines.

The detailed report of this study is provided in Appendix H.

2. **Freshwater Fish Acute Toxicity (Rainbow Trout)**

The acute toxicity of Orlistat to Rainbow Trout (Oncorhynchus mykiss), a cold-freshwater fish, was conducted under static conditions according to the FDA Environmental Assessment Technical Assistance 4.11.

Twenty fish per each treatment concentration having a mean weight of 0.99 grams and a mean standard length of [redacted] were exposed for 96 hours. In a definitive test, the nominal concentrations of 1.56, 2.59, 4.32, 7.20, 12.00, and 20.0 mg/L were utilized. The test concentrations were analytically quantified from samples collected at 0, 48, and 96 hours. The mean measured concentrations were [redacted], representing [redacted] of the expected nominal concentrations. The 96-hour median lethal concentration ($LC_{50}$), the concentration of Orlistat estimated to be lethal to [redacted] percent of the test population was calculated to be greater than [redacted] mg/L. The NOEC was [redacted] mg/L. This study was conducted according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix I.

3. Microbial Growth Inhibition Study

The Minimum Inhibitory Concentrations (MIC) of Orlistat were determined according to the FDA Environmental Assessment Technical Assistance 4.02.

The organisms utilized in this study were free living nitrogen fixing bacteria (Azotobacter chroococcum), bacterium (Bacillus megaterium), soil bacteria (Pseudomonas fluorescens), nitrogen fixing blue-green alga (Anabaena flos-aquae), fungus (Penicillium canescens, and Chaetomium globosum) and mold (Aspergillus clavatus). No inhibition of growth was observed for all organisms at any concentration of Ro 18-0647 tested up to and including [redacted] This study was conducted according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix J.

4. Activated Sludge Respiration Inhibition Study

Orlistat was tested in the activated sludge respiration inhibition test according to the Organisation for Economic Co-operation and Development (OECD) Guideline reference #209.

The respiration rate of an activated sludge and synthetic sewage aerated for [redacted] hours in the presence of test substance was compared to the respiration rate of control to which no substance was added. The respiration rate was measured in the presence of Ro 18-0647 at

concentrations ranged from 2.5, 5.0, 10, 25, and 50 mg/L, resulting in percent inhibition value of 2.97, 76.50, 13.40, 0.00 and 13.4% respectively. The percent inhibition value of [redacted] was not used in the calculation due to improper aeration. An $EC_{50}$ (the concentration of the test substance at which the respiration rate of the activated sludge is [redacted]% of that shown by the control) for Ro 18-0647 could not be calculated since no trend exists for the inhibition, and the inhibition in all concentrations was [redacted] than [redacted]%. Therefore, it can be concluded that Ro 18-0647 is not inhibitory between 2.5 and 50 mg/L to the aerobic respiration of microbes in an activated sludge. This study was conducted according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix K.

5. Aerobic Biodegradation in Water

Ro 18-0647 was tested for biodegradability in an aqueous medium at a test concentration of [redacted] mg carbon/L according to the FDA Environmental Assessment Technical Assistance 3.11.

The aqueous medium consisted of a composite inoculum of activated sludge and secondary effluent, mineral salt media and yeast extract. The production of carbon dioxide was measured at various intervals over a period of 29 days. For the test chemical, approximately 18.4% (5.4, 38.7 and 11.00% in replicates 1, 2, and 3) of the applied carbon 14 activity was mineralized to carbon dioxide during the 29-day test period. After the 29-day incubation, approximately 93% of the applied carbon 14 glucose (reference chemical) was mineralized to carbon dioxide. Therefore, under the conditions and criteria of the test, Ro 18-0647 was considered not readily biodegradable in an aqueous medium. This study was conducted according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix L.

6. Freshwater Green Alga Acute Toxicity Study

The freshwater green alga (Selenastrum capricornutum) acute toxicity study was conducted under static conditions according to the FDA Environmental Assessment Technical Assistance 4.01.

The definitive study was conducted at nominal test concentrations of 0.63, 1.25, 2.50, 5.00, 10.20 and 20.00 mg/L. The measured

concentrations were [redacted]. Measured concentrations decreased dramatically during the 10-day exposure period probably due to the insolubility of test article resulting from pH shifts, adsorption to algae and glassware, and/or by the test article degradation during the exposure period. The NOEC of Ro 18-0647 was [redacted] based upon the mean of maximum standing crop. This study was conducted according to the FDA GLP Guidelines.

The detailed report of the study is included in Appendix M.

## THE MAXIMUM EXPECTED EMITTED CONCENTRATION (MEEC) OF ORLISTAT

The Maximum Expected Emitted Concentration (MEEC) of Orlistat and/or its metabolites in US domestic waste may be estimated from the assumed daily average per capita amount of Orlistat used and the estimated average per capita volume of water containing these materials. The estimated MEEC value is [redacted] The estimated Expected Environmental Concentration (EEC) is [redacted] ppm with the assumption of depletion due to aquatic biodegradation processes assumed to be zero as a worst case scenario. The estimation of MEEC and EEC is shown in Appendix F.

Based on the aquatic effects studies, the assessment factor of [redacted] than [redacted] was observed based on Daphnia $EC_{50}$ value of [redacted]. The assessment factor of greater than [redacted] was observed based on the no-observed effects concentration (NOEC) for algae. **Therefore, it is concluded that this drug is not likely to cause any deleterious adverse effects to aquatic organisms through its usage.**

### 7. (v)(c) Terrestrial Ecosystems

**The drug is not likely to be released in terrestrial ecosystems either through usage or during the manufacturing process, therefore, it is not likely to cause any detrimental effects in terrestrial ecosystems.**

All solid/liquid waste generated during manufacturing will be incinerated and/or disposed in a lined industrial landfill. The drug and its metabolites will primarily be released in the aqueous environment through usage.

Animal studies have indicated relatively low toxicity. The acute oral $LD_{50}$ for rats is greater than [redacted] indicating relatively low acute toxicity. Orlistat is not a mutagen in various mutagenic tests. It is not

a teratogen or reproductive toxicant ( MSDS, Appendix A). **Therefore, it is expected that the drug is not likely to cause significant impact in the terrestrial ecosystems if released accidentally and/or due to minute (PPT range) concentration in the reclaimed sludge.**

Soil Adsorption/Desorption Study: Soil adsorption/desorption studies were conducted on Orlistat according to the FDA Environmental Assessment Technical Assistance 3.08.

Three different types of soil (silt loam, clay loam and loam) were used in this study. The calculated $K_d$ values were [redacted] for silt loam, clay loam and loam, respectively. The calculated $K_{oc}$ values were [redacted] for silt loam, clay loam and loam, respectively. **Therefore, under the conditions and criteria of the test, Orlistat was characterized as being immobile in all soils tested.** This study was concluded according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix N.

Earthworm Subacute Toxicity Study: Earthworm Subacute Study with Orlistat using nightcrawler (Lumbricus terrestris) was conducted. In a fourteen day range finding test there was no mortality observed at soil concentrations ranging from 0.15 to 999 mg/kg of dry soil weight. Therefore, a definitive study was conducted at a single concentration of 1,000 mg/kg of Orlistat per dry soil. There was statistically significant mortality observed in the treatment animals during the course of the test. The mortality did exceed fifty percent of the population. The design and results of the test preclude an accurate calculation of the $LC_{50}$ concentration. The mortality and weight loss were likely due to a synergistic effect between the soil pH and the test article. The $LC_{50}$ value for Orlistat is approximately 969 mg active ingredient (ai)/kg of dry soil based on the average maximum measured concentration and is approximately 907 mg ai/kg based on the grand mean concentration. The exposed worms lost a statistically significant amount of weight as compared to the control animals. This study was concluded according to the FDA GLP Guidelines.

The detailed report of this study is included in Appendix O.

**Based on the above discussion and study results, it is concluded that the drug is not likely to cause any significant detrimental effects in terrestrial ecosystems.**

## 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTRATES

The primary impact from the use of Orlistat will be the disposition of the drug subsequent to oral administration. The discharge of human excreta containing drug product residues and/or its metabolites will be handled by conventional sewage disposal systems in accord with federal, state, and local regulations. Furthermore, Orlistat will be prescribed in milligram quantities by a licensed practitioner; consequently its distribution will be controlled. **Therefore, its use will not be indiscriminate and will not adversely affect, to a significant extent, the quality of the environment.**

A secondary environmental consequence results from the minor discharge of manufacturing pollutants to air and water during manufacturing. Such discharge will also be in accord with all federal, state, and local requirements.

### 8.1 Air

The physical-chemical and environmental effects data reported in item 7, as well as the controls exercised at the site of manufacture of drug substance and drug product, indicate that insignificant concentrations of Orlistat in ambient air will result from the use and/or disposal of Orlistat. The potential health effects on humans from exposure to Orlistat are limited to occupational exposure. As mentioned under OSHA regulated compounds, appropriate engineering and protective equipment controls will be used to protect employees.

### 8.2 Freshwater Estuarine and Marine Ecosystems

In order to evaluate the impact of the very low concentration of Orlistat expected to enter the aquatic environment, a number of studies described in item 7 were conducted. The following is the summary of environmental effects data.

## RESULTS SUMMARY OF ENVIRONMENTAL EFFECTS STUDIES

| [illegible] | [illegible] ppm | [illegible] ppm |
|---|---|---|
| Daphnia Magna (static) | 1.9 | 6.92 |
| Rainbow Trout (static) | 18.5 | >18.5 |
| Microbial Inhibition. (4.02) | 10.00 | >10 |
| Activated Sludge | 50.00 | >50.00 |
| Green Algae | 1.92 | >1.92 |
| Earth Worm (subacute) | | ~969 |

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The estimated EEC, EIC and MEEC values are provided in Appendix F (confidential). The results of effects studies reported above indicate that the EEC of Orlistat arising from product use should not have an unfavorable environmental impact on aquatic life, since the lowest aquatic NOEC (1.9 Daphnia and Green Algae value as shown in the above table) is greater than the EEC by a factor of approximately [redacted] **This value is greater than the assessment factor of [redacted] for test [redacted] described in the FDA's Guidance Document which clearly indicates that no significant effects are likely to be observed in the aquatic environment.**

### 8.3 Terrestrial Ecosystem

As mentioned under item 7, the exposure to human or animals is not likely to occur during the manufacturing or through usage of the drug. Furthermore, the preliminary results of the earthworm subacute toxicity study indicate that the $LC_{50}$ is approximately 969 mg/kg. The soil adsorption/desorption study suggests that it is immobile. **Based on these studies it is expected that no significant detrimental effects are likely to occur on terrestrial life.**

## 9. USE OF RESOURCES AND ENERGY

9. A Natural Resources and Energy The maximum annual production of the drug substance for the U.S. market over the five year period following introduction and natural resources and energy information is provided in confidential Appendix E.

Based on these figures and the estimated maximum 5-year production volume of Xenical drug product, the additional utilization due to the manufacture of the Xenical drug product will be [redacted] of the total.

The facility used for production of Xenical drug product is already committed to the production of other Pharmaceuticals and Vitamins and Fine Chemicals. Therefore, the production of Xenical would have no significant impact on energy utilizations or on the surrounding environment.

9. B Effect on Endangered or Threatened Species There are no effects expected upon endangered or threatened species due to the proposed action.

9. C Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places There are no effects expected upon property listed in or eligible for listing in the National Register of Historic Places due to the proposed action.

## 10. MITIGATION MEASURES

**Environmental impacts associated with the production of Xenical will be avoided or mitigated by the use of appropriate control measures in accord with all federal, state, and local regulations.**

Air emissions control devices include vent condensers, scrubbers and fabric filter dust collectors. Environmental impacts associated with the disposition of drug substance and/or metabolites following consumption in humans will be mitigated by conventional wastewater treatment plants. All rejected Xenical drug product will be disposed by incineration. Unused or out-of-date product is returned to Roche/Nutley for credit and disposed in the same manner.

Waste minimization is considered in the design of Hoffmann-La Roche processes to the fullest exter possible while maintaining the quality and purity of the manufactured drug substance. Solvents are recovered and reused within the same process or for a different product depending on quality control specifications. Yield maximization is an important factor at all stages of pilot plant and process development.

Chapter 7:1E of the New Jersey Administrative Code covers Discharge of Petroleum and other Hazardous Substances. The Hoffmann-La Roche Nutley facility is classed as a major facility under this regulation and as such is required to maintain plans for Discharge Prevention, Containment and Countermeasures (DPCC) and Discharge, Cleanup and Removal (DCR) acceptable to the New Jersey Department of Environmental Protection and Energy (NJDEPE). In addition to the physical facilities for containment of spills which are described in the DPCC plan, three emergency squads have been established at the Nutley site:

1. Roche Environmental Response Squad (ERS)

2. Roche Fire Brigade

3. Roche Medical/Heavy Rescue Squad

The squads consist of over 90 volunteers from various departments within Roche who respond to emergencies and actively participate in monthly training drills, as well as semiannual joint emergency drills with Clifton and Nutley Local Emergency Planning Committee's (LEPC).

The Roche Environmental Response Squad (ERS) currently consists of 28 highly trained individuals who deal immediately and effectively with air, land, and water spills of hazardous substances, at the Nutley plant. The team also lends its assistance to our LEPC's and other Roche facilities. It consists of representatives from plant-wide activities maintaining a balance of technical and skilled personnel from various plant activities, i.e., tank farm, boiler operations, wastewater treatment, chemical processing, warehousing, and laboratories.

The ERS works closely with the other emergency squads and the Chemical Production Department (CPD) personnel in order to effectively deal with environmental emergency situations.

## 11. ALTERNATIVES TO THE PROPOSED ACTION

The FDA has two alternatives by which to respond to this proposed action:

- Approval of the proposed action through the issuance of Finding of No Significant Impact (FONSI)
- Non-approval and notification of intent to prepare an Environmental Impact Statement (EIS)

**We believe that the first action, issuance of a FONSI, is fully justified by this Environmental Assessment. Manufacturing operations will be in compliance with the regulations of the applicable governmental agencies. Releases of Orlistat to the environment will be mitigated as discussed in Item 10. Fate and effects testing (described in Sections 7 and 8) support the position that the manufacture and use of Orlistat will not produce an adverse effect on the environment.**

**Approval of the proposed action will make available to the physician a significantly valuable, relatively safe with limited unwarranted side effects and environmentally safe drug in the treatment of obesity.**

## 12. LIST OF PREPARERS

Annette Bucca-Janacek, B.A., B.S.
Associate Environmental and Safety Affairs Professional
Corporate Environmental and Safety Affairs

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